

### **Amendments to the Claims:**

The listing of claims will replace all prior versions, and listings, of claims in the application:

### **Listing of Claims:**

1. (Original) A modified release pharmaceutical composition comprising at least one form of tramadol selected from the group consisting of tramadol, enantiomers thereof, pharmaceutically acceptable salts thereof and combinations thereof, wherein the composition, when orally administered to a patient, induces a statistically significant lower mean fluctuation index in the plasma than an immediate release composition of at least one form of tramadol while maintaining bioavailability substantially equivalent to that of the immediate release composition.
  
2. (Original) A modified release pharmaceutical composition comprising at least one form of tramadol selected from the group consisting of tramadol, enantiomers thereof, pharmaceutically acceptable salts thereof and combinations thereof, wherein the composition, when orally administered to a patient, produces a mean maximum plasma concentration ( $C_{\max}$ ) of the at least one form of tramadol that is lower than that produced by an immediate release pharmaceutical composition of the at least one form of tramadol, and the area under the concentration-time curve (AUC) and the mean minimum plasma concentration ( $C_{\min}$ ) are substantially equivalent to that of the immediate release pharmaceuticals composition.

3. (Original) A modified release pharmaceutical composition comprising at least one form of tramadol selected from the group consisting of tramadol, enantiomers thereof, pharmaceutically acceptable salts thereof and combinations thereof, wherein the compositions, when orally administered to a patient, produces a mean maximum plasma concentration ( $C_{max}$ ) of the at least one form of tramadol and an area under a plasma concentration vs. time curve (AUC) within the range of from about -20% to about +25 of that produced by an immediate release pharmaceutical composition of the at least one form of tramadol.

4. (Currently Amended) The pharmaceutical composition of Claim 1 ~~2- or 3-~~ wherein the at least one form of tramadol is tramadol hydrochloride and the immediate release pharmaceutical composition is the subject of the United States Food and Drug Administration Approved New Drug Application number N20281.

5. (Original) A modified release pharmaceutical composition comprising at least one form of tramadol selected from the group consisting of tramadol, enantiomers thereof, pharmaceutically acceptable salts thereof and combinations thereof, wherein the compositions exhibits an *in vitro* dissolution profile (measured using the USP Basket Method at 75 rpm in 900 ml 0.1 N HCl at 37°C) such that after 2 hours, from about 0% up to about 30% (by weight) of the at least one form of tramadol is released, after 4 hours, from about 5% to about 55% (by weight) of the at least one form of tramadol is released, after 12 hours, more

than about 50% (by weight) of the least one form of tramadol is released, and after 24 hours, more than about 80% (by weight) of the at least one form of tramadol is released.

6. (Original) A modified release pharmaceutical composition comprising at least one form of tramadol selected from the group consisting of tramadol, enantiomers thereof, pharmaceutically acceptable salts thereof and combinations thereof, the composition exhibits an *in vitro* dissolution profile (measured using the USP Basket Method at 75 rpm in 900 ml 0.1 N HCl at 37°C) such that after 2 hours, from about 0% up to about 30% (by weight) of the at least one form of tramadol is released, after 4 hours, from about 5% to about 22% (by weight) of the at least one form of tramadol is released, after 6 hours, from about 15% to about 30% (by weight) of the least one form of tramadol is released, and after 8 hours, more than about 40% (by weight) of the at least one form of tramadol is released.

7. (Original) The modified release pharmaceutical composition of Claim 6 the composition exhibits an *in vitro* dissolution profile (measured using the USP Basket Method at 75 rpm in 900 ml 0.1 N HCl at 37°C) such that after 2 hours, from about 2% up to about 10% of the at least one form of tramadol is released, after 4 hours, from about 12% to about 20% of the at least one form of tramadol is released, after 6 hours, from about 30% to about 38% of the least one form of tramadol is released, and after 8 hours, from about 48% to about 56% of the at

least one form of tramadol is released, and after 12 hours, more than about 76% of the at least one form of tramadol is released.

8. (Original) A modified release pharmaceutical composition comprising at least one form of tramadol selected from the group consisting of tramadol, enantiomers thereof, pharmaceutically acceptable salts thereof and combinations thereof, wherein the pharmaceutical composition, when orally administered to a patient, provides a mean maximum plasma concentration ( $C_{\max}$ ) of the at least one form of tramadol from about 80 ng/ml to about 500 ng/ml.

9. (Original) A modified release pharmaceutical composition comprising at least one form of tramadol selected from the group consisting of tramadol, enantiomers thereof, pharmaceutically acceptable salts thereof and combinations thereof, wherein the pharmaceutical composition, when orally administered to a patient, provides a time to mean maximum plasma concentration ( $T_{\max}$ ) of the at least one form of tramadol from about 4 hours to about 14 hours.

10. (Original) A modified release pharmaceutical composition comprising at least one form of tramadol selected from the group consisting of tramadol, enantiomers thereof, pharmaceutically acceptable salts thereof and combinations thereof, wherein the pharmaceutical composition, when orally

administered to a patient, provides a plasma concentration time curve with an area under the curve ranging from about 1000 ng.hr/ml to about 1000 ng.hr/ml.

11. (Original) A modified release pharmaceutical composition comprising:

(i) a core comprising at least one form of tramadol selected from the group consisting of tramadol, enantiomers thereof, pharmaceutically acceptable salts thereof and combinations thereof and at least one pharmaceutically acceptable excipient; and

(ii) a coating comprising at least one water-insoluble, water permeable film-forming polymer, at least one plasticizer and at least one water-soluble polymer.

12. (Original) The modified release pharmaceutical composition of claim 11, wherein the proportion of the at least one water-insoluble, water-permeable film-forming polymer varies from about 20% to about 90% of the coating dry weight, the proportion of the at least one plasticizer varies from about 5% to about 30% of the coating dry weight, and the proportion of the at least one water-soluble polymer varies from about 10% to about 75% of the coat dry weight.

13. (Original) The modified release pharmaceutical composition of claim 11, wherein the at least one water-insoluble, water-permeable film-forming polymer is ethylcellulose.

14. (Original) The modified release pharmaceutical composition of claim 11, wherein the at least one water-insoluble polymer is polyvinylpyrrolidone.
15. (Original) The modified release pharmaceutical composition of claim 11, wherein the at least plasticizer is dibutyl sebacate.
16. (Original) The modified release pharmaceutical composition of claim 11, wherein the at least one water-insoluble, water-permeable film-forming polymer is ethylcellulose, the at least one water-soluble polymer is polyvinylpyrrolidone and the at least one plasticizer is dibutyl sebacate.
17. (Original) The modified release pharmaceutical composition of claim 11, wherein the at least one pharmaceutically acceptable excipient in the core is selected from the group consisting of at least one lubricant, at least one binder, at least one glidant and combinations thereof.
18. (Original) The modified release pharmaceutical composition of claim 16, wherein the at least one pharmaceutically acceptable excipient in the core is selected from the group consisting of at least one lubricant, at least one binder, at least one glidant and combinations thereof.
19. (Original) The modified release pharmaceutical composition of claim 17, wherein the at least one lubricant is sodium stearyl fumarate, the at least one binder is polyvinyl alcohol, and at least one glidant is colloidal silicon dioxide.

20. (Original) The modified release pharmaceutical composition of claim 18, wherein the at least one lubricant is sodium stearyl fumarate, the at least one binder is polyvinyl alcohol, and at least one glidant is colloidal silicon dioxide.

21. (Original) The modified release pharmaceutical composition of claim 11, wherein the at least one form of tramadol is tramadol hydrochloride and wherein the tramadol hydrochloride is present in an amount of from about 50 mg to about 400 mg.

22. (Original) The modified release pharmaceutical composition of claim 16, wherein the at least one form of tramadol is tramadol hydrochloride and wherein the tramadol hydrochloride is present in an amount of from about 50 mg to about 400 mg.

23. (Original) The modified release pharmaceutical composition of claim 19, wherein the at least one form of tramadol is tramadol hydrochloride and wherein the tramadol hydrochloride is present in an amount of from about 50 mg to about 400 mg.

24. (Original) The modified release pharmaceutical composition of claim 20, wherein the at least one form of tramadol is tramadol hydrochloride and wherein the tramadol hydrochloride is present in an amount of from about 50 mg to about 400 mg.

25. (Original) The modified release pharmaceutical composition of claim 24, wherein the composition is in the form of a tablet.

26. (Original) A modified release pharmaceutical composition comprising:

(i) a core comprising tramadol hydrochloride, polyvinyl alcohol, colloidal silicon dioxide and sodium stearyl fumarate; and

(ii) a coating comprising ethylcellulose, polyvinylpyrrolidone and dibutyl sebacate.

27. (Original) The modified release pharmaceutical composition of claim 26, wherein the at least one form of tramadol is tramadol hydrochloride and wherein the tramadol hydrochloride is present in an amount of from about 50 mg to about 400 mg.

28. (Original) The modified release pharmaceutical composition of claim 27, wherein the composition is in the form of a tablet.